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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/659,579	GULATI, ANIL	
	Examiner	Art Unit	
	Abigail M. Cotton	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *3,5,6,8,10-12,16-18 and 26-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,7,9,13-15 and 19-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/2/2004 and 4/8/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the remarks filed March 20, 2007. Claims 1-30 are pending in the application, with claims 3, 5-6, 8, 10-12, 16-18 and 26-30 having been withdrawn as drawn to a non-elected invention and/or species of invention. Accordingly, claims 1-2, 4, 7, 9, 13-15 and 19-25 are being examined on the merits herein.

It is noted that the claims are being examined only to the extent they read on the elected group of endothelin antagonist that is a mixed ET_A/ET_B endothelin antagonist. It is furthermore notes that the claims are only being examined to the extent they read on the elected species of ET_A/ET_B endothelin antagonist that is bosentan, and the elected species of therapeutic agent that is the cholinesterase inhibitor tacrine, as elected by Applicants in the response filed March 20, 2007. The requirement for the election of a particular disease state is being withdrawn, as a search for the treatment of all of Alzheimer's or a dementia of vascular origin does not pose an undue burden. Accordingly, the claims have been examined to their full extent with regards to the treatment of the disease states recited therein.

Priority

Applicant's claim of priority to U.S. Provisional Application Serial No. 60/413,539 filed September 25, 2002, is acknowledged.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02. In particular, the oath or declaration is defective because the specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 602.

Election/Restrictions

Applicant's election with traverse of the claims of Group I, namely claims 1-2 (in part), 4 (in part), 7 and 9-25 (in part), drawn to methods with mixed ET_A/ET_B endothelin antagonists, in the reply filed on March 20, 2007 is acknowledged. The traversal is on the grounds that a search for groups I-IV would not pose an undue burden, because a search for one type of endothelin antagonist would encompass the other types of endothelin antagonists. This is not found persuasive because a search for the claimed methods of treatment including all of the different types of antagonists as claimed,

across all applicable classes and subclasses, is deemed to pose an unacceptable search burden on the office. Accordingly, claims 3, 5-6, 8 and 26-30 are being withdrawn as drawn to a non-elected invention.

Applicants' election of the species of the specific endothelin antagonist that is bosentan and the specific second therapeutic agent that is a cholinesterase inhibitor (tacrine), is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the species restriction requirement, the species election has been treated as an election without traverse (MPEP § 818.03(a)). Accordingly, claims 10-12 and 16-18 are withdrawn as being drawn to a non-elected species of invention.

The requirement for election of a single species of disease is being withdrawn, as discussed above, as the search for all claimed diseases is not deemed to pose an undue burden.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 4, 7, 9, 13-15 and 19-25 are rejected under 35 U.S.C. 112, first paragraph, for lacking enablement for the full scope of the claims. The specification is enabling for a method of blocking systemic hemodynamic and regional circulatory effects in normotensive rats with the specific ET_A receptor antagonist that is BQ123, for example. However, the specification is not enabling for the treatment of Alzheimer's disease or all dementias of vascular origin, in any mammal, with any of the numerous and diverse compounds corresponding to mixed ET_A/ET_B endothelin antagonists, as recited in claim 1, which includes those numerous and diverse compounds listed in Appendix B, as recited in claim 7.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set fourth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. The nature of the invention and scope of the claims: The instant invention pertains to method of treating Alzheimer's disease or any dementia of vascular origin, by administering to any mammal any of the numerous and diverse compounds having mixed ET_A/ET_B antagonist activity, as recited in claim 1. It is furthermore noted that the claims read on treatment for all conditions in the dementia is of vascular origin, as well as any compound having mixed ET_A/ET_B antagonist activity, including those specifically disclosed by Applicants as well as any other conditions and/or compounds that are yet to be discovered.

The broad scope of the invention is exacerbated by the fact that the claims include treatment with any of the compounds having mixed ET_A/ET_B endothelin antagonist, which include numerous and diverse compounds having widely varying structures, such as those disclosed in Appendix B. For example, compound 46 (bosentan) has two aromatic rings that are doubly substituted with nitrogen, whereas compound 48 contains aromatic cyclic structures that are not substituted by a heteroatom. Thus, the compounds are classified in numerous different subclasses across class 514, for example, and thus are not expected to have similar chemical reactivities or biochemical functions of those of ordinary skill in the art.

2. The state of the prior art: The state of the prior art is that the treatment of Alzheimer's disease is a complex and chronic disease state that has represented a

major challenges to academic and pharmaceutical research efforts (see article entitled "Alzheimer's Disease and Related Dementias: Prospects for Treatment by Williams et al, 1997, Exp. Opin. Invest. Drugs, Vol. 6, No. 6, pages 735-757.) While current treatments include second generation acetylcholinesterase inhibitors, such as donepexil, but such drugs offer only palliative treatment (see abstract of Williams et al, in particular.) The state of the art in the treatment of Alzheimer's indicates that the lack of animal models for the disease remains a large roadblock in finding treatments. In particular, the art teaches "the clinical development of these compounds is hindered by the lack of a widely available animal model which mimics the pathology of AD" (Sheryl J. Hays, "Alzheimer's Disease and Beta-Amyloid Patent Activity between May 1995 and July 1996, Exp. Opin. Ther. Patents, 1996, Vol. 6, No. 10, pages 1035-1046, abstract.) A problem with the development of such *in vivo* models being that such models have to take into account the multifactorial nature of the disease state, as opposed to amyloid neurotoxicity specifically, which "may or may not be causative (see Williams et al, abstract, in particular.) The article entitled "Commentary: Amyloid-Beta Deposits: Can you take them to the Bank?" by Patrick C. May, discloses that much drug development is focused on the fact that "'bad things' are associated with the production and/or accumulation of A-beta peptide and by limiting its production, a therapeutic benefit will be achieved inn AD" (see abstract, in particular.) However, May goes on to disclose that efforts to model this aspect of AD in vivo have so far yielded "ambiguous results" (see abstract, in particular.) Thus, the prior art teaches that treatments for Alzheimer's are as yet unsatisfactory, as the disease is complex and the complete etiology is not yet

known. Furthermore, the evaluation of new treatments remains difficult as acceptable animal models for the disease are not as yet known, and mere tests for alleviating amyloid neurotoxicity yield at best ambiguous results in proposed animal models. Accordingly, the state of the art indicates that it is not known whether the decline of neurotoxicity of Beta-amyloid *in vitro* is predictive of the treatment of the Alzheimer's disease in a patient, as claimed by Applicants.

Furthermore, as discussed above, the numerous and diverse compounds recited in the claims are classified in various different subclasses across class 514, for example, and thus are not expected to have similar chemical reactivities or biochemical functions of those of ordinary skill in the art. Thus, it is not known in the art that all compounds having mixed ET_A/ET_B endothelin antagonist activity, such as those disclosed in Appendix B, would have the same or similar biochemical functions as one another, such as Beta-amyloid neurotoxicity reduction.

3. The relative skill of those in the art: The relative skill in the art is fairly high, with the typical practitioner having a medical degree and/or an advanced degree in the biochemical, chemistry or pharmaceutical-related arts.

4. The predictability of the art: Note that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 166 USPQ 198 indicates that the more unpredictable an area is,

the more specific enablement is necessary in order to satisfy the statute. Furthermore, with regards to the *in vivo* treatment of conditions based on *in vitro* activity, it is noted that the correlation between any demonstrated *in vitro* activity and actual *in vivo* treatment is highly unpredictable, absent any known *in vitro* models for such conditions (see MPEP § 2164.)

With regards to the treatment of Alzheimer's disease it is noted that, as discussed above, the development of suitable *in vivo* animal models has hindered the development of new drugs, and drug candidates selected on the basis of *in vitro* studies on beta-amyloid toxicity have not shown efficacy in the treatment of proposed AD models (see abstract of May, in particular.) For example, May teaches that there are "numerous in vitro studies documenting the neurotoxic and proinflammatory properties of Aß peptide ...[h]owever efforts to model this aspect of AD in vivo either by direct injection of Aß peptide or through the generation of APP over-expressing transgenic animal models have so far yielded ambiguous results" (see abstract, in particular.)

Accordingly, it is highly unpredictable whether a compound that shows *in vitro* activity for the reduction of Beta-amyloid neurotoxicity will show any actual beneficial effect for the treatment of the Alzheimer's disease state *in vivo*. The treatment of Alzheimer's disease is also highly unpredictable, given the fact that the full etiology of the disease is not known.

5. The amount of direction or guidance presented: The Specification discloses that it has been theorized that increasing concentrations of Beta-amyloid protein, a feature of Alzheimer's disease, can contribute to AD pathology by inducing microvasculture vasoconstriction and reducing cerebral blood flow. The Specification also discloses that that beta-amyloid can enhance vasoactivity by inducing endothelin-1, which is believed to act as a neuromodulator by causing a severe reduction of the cerebral blood flow (see pages 2-3 of Specification.) Accordingly, compounds having endothelin antagonist activity are believed to be useful for the treatment of Alzheimer's disease and dementias of vascular origin (see page 3, in particular.) The Specification does not disclose that drugs that act as endothelin antagonists are known in the art to be useful for the treatment of Alzheimer's disease, or teach how antagonism of endothelin *in vitro* or *in vivo* animal models could be directly correlated with the treatment of Alzheimer's. Accordingly, the specification does not provide adequate guidance as to the treatment of Alzheimer's in all mammals with endothelin antagonists in general.

Furthermore, it is noted that the recitation of an "endothelin antagonist" is considered to be functional language. Functional language at the point of novelty, as herein employed by Applicants, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997) at 1406: stating this usage does "little more than outline the goal appellants hope the recited invention achieves and the problems the invention will hopefully ameliorate." The CAFC further clearly states that "[A] written

description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405 (emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus ..." at 1406 (emphasis added.)

Thus, Applicant's functional language at the points of novelty fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph. Claims employing functional language at the exact point of novelty, such as Applicants', neither provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938).)

6. The presence or absence of working examples: the specification shows an example of blocking of the systemic hemodynamic and regional circulatory effects of ET-1 in male normotensive Sprague-Dawley rats with the specific ET_A receptor antagonist that is BQ123 (see page 11, in particular.) The specification also shows an example of the increase of vascular resistance and altered response to ET-1 that occurs with beta-amyloid protein in rats (see page 14, lines 1-13, in particular), as well as the

increased expression of ET-1 in Aβ-treated rats (see page 14, lines 14-23 and pages 20-22 in particular.) The specification concludes that Aβ increases the endogenous concentration of ET-1, leading to vasoconstriction, and that administration of the ET-1 antagonist can thereby provide treatment by causing a rebound in blood flow (see page 22, lines 1-10, in particular.) However, it is noted that the specification does not provide working examples that show a rebound in blood flow for all or a representative number of compounds having endothelin antagonist activity, including those listed in the appendices as well as all other ET antagonist compounds. The specification does not even show examples demonstrating that all of the compounds listed in the appendices even have endothelin antagonist activity *in vitro*. The specification also does not show any examples correlating such improved blood flow to actual treatment, *in vivo* of individuals having Alzheimer's disease. The specification further does not provide working examples of treatment in any animal models or other models known to be predictive of success in the treatment of Alzheimer's disease, or show how Alzheimer's disease could be recognized and treated in non-human mammals. Accordingly, the specification does not provide working examples showing treatment or results predictive of treatment of Alzheimer's in any mammal with any of the endothelin antagonists as claimed.

(7) The quantity of experimentation necessary: In light of the above, it is considered that a skilled artisan would have to exercise **undue experimentation** to practice the instant invention.

In particular, as the correlation between endothelin antagonism and/or increased blood flow due to endothelin antagonism and the treatment of Alzheimer's disease is not known, the skilled practitioner would have to test each and every one of the compounds as claimed, or at least a subset that is sufficiently representative of the compounds, to determine treatment efficacy for each condition. For example, to test for treatment of the disease, a one of the compounds meeting the limitations of the claims would have to be selected, and a dosage regimen (dose amount, frequency, route of administration) selected. If efficacy of the drug did not result, the dosage regime would have to be varied, for example by changing the dosage amount or route of administration, until efficacy was achieved. If no animal model of Alzheimer's is available for testing, then toxicity trials would have to be conducted before such testing could be conducted in humans to determine appropriate toxicity levels. If efficacy in the treatment of Alzheimer's was shown with a particular compound, another compound meeting the limitations of the claims would have to be selected and the process would have to be repeated, including determining the optimum dosage regimen and animal model and/or toxicity levels for evaluation. Once efficacy was established for all or a representative sample of the compounds as claimed for the particular condition, the process would have to be repeated for at least the other conditions disclosed by Applicants. Also, methods would have to be developed to recognize the Alzheimer's disease state in non-human mammals, and the compounds would have to be again tested with in such non-human mammals, in order to fully enable the scope of the claims. Thus, the skilled

artisan would have to undergo exhaustive studies to evaluate each of the claimed compounds for the treatment of Alzheimer's and any other dementia having a vascular origin in any mammal, in order to be able to fully carry out the invention commensurate in scope with the claims.

Furthermore, the artisan would have to perform additional scientific research to determine all of those conditions that are dementias of vascular origin, as well as all endothelin antagonists, known and unknown, and which could be used to treat the claimed conditions. For example, the artisan would have to evaluate all currently-known dementias to determine whether they can be treated with the compounds, which would required exhaustive research such as that described above, as well as evaluate new compounds to determine whether they have endothelin antagonist activity.

Accordingly, it is considered that the skilled artisan would have to exercise **undue experimentation** to fully practice the instant invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for a search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the *Wands* factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of ordinary skill in the art would have to engage in *undue experimentation* to test all of the compounds as claimed for all of the possible conditions, with no reasonable assurance of success.

Claims 1-2, 4, 7, 9, 13-15 and 19-25 are *further* rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of blocking systemic hemodynamic and regional circulatory effects in normotensive rats with the specific ET_A receptor antagonist that is BQ123, for example, does not reasonably enable one of ordinary skill in the art to provide *prophylactic treatment*, i.e. prevent, Alzheimer's disease or a dementia of vascular origin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Foreman*, 230 USPQ 546 (Board of Appeals 1986) at 547, the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art: (5) the breadth of the

claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation that is necessary.

(1) *The Nature of the Invention:*

The invention is drawn to "a method of treating Alzheimer's disease or a dementia of vascular origin" by administering a therapeutically effective amount of an endothelin antagonist, as claimed. It is noted that Applicants' have defined the term "treatment" as including "both medical therapeutic and/or prophylactic administration" (see page 6, lines 11-13), and thus the claims encompass methods of *preventing* onset of Alzheimer's or dementia of vascular origin with any of the numerous and diverse compounds as claimed.

(2) *Breadth of the Claims:*

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claimed invention includes the prevention of Alzheimer's and dementias of vascular origin. The term "prevention" indicates a claim whereby those normally not at risk for developing such a disorder would be prevented from ever developing the Alzheimer's or dementia of vascular origin with any of the numerous compounds claimed.

(3) *Guidance of the Specification:*

The guidance of the specification as to "prevention" of Alzheimer's or dementia of vascular origin is completely lacking. As discussed above, the specification discloses that it has been theorized that increasing concentrations of Beta-amyloid protein, a feature of Alzheimer's disease, can contribute to AD pathology by inducing microvasculture vasoconstriction and reducing cerebral blood flow. The Specification also discloses that that beta-amyloid can enhance vasoactivity by inducing endothelin-1, which is believed to act as a neuromodulator by causing a severe reduction of the cerebral blood flow (see pages 2-3 of Specification.) The specification thus postulates that compounds having endothelin antagonist activity are believed to be useful for the treatment of Alzheimer's disease and dementias of vascular origin (see page 3, in particular.) The specification also shows an example of blocking of the systemic hemodynamic and regional circulatory effects of ET-1 in male normotensive Sprague-Dawley rats with the specific ET_A receptor antagonist that is BQ123 (see page 11, in particular.) The specification also shows an example of the increase of vascular resistance and altered response to ET-1 that occurs with beta-amyloid protein in rats (see page 14, lines 1-13, in particular), as well as the increased expression of ET-1 in Aβ-treated rats (see page 14, lines 14-23 and pages 20-22 in particular.) However, the examples do not show that the effects of the particular antagonist are sufficient to *prevent* the occurrence either Alzheimer's or dementias of vascular origin, and does not link such experiments to models of Alzheimer or dementia prevention. The specification

also does not teach means by which the *prevention* of Alzheimer's or dementias of vascular origin could be evaluated, for example the specification does not provide models for evaluation prevention of Alzheimer's or dementias of vascular origin. Thus, the specification does not provide any information regarding the complete *prevention* of Alzheimer's disease or dementias of vascular origin in a population, as would be required by a claim for prevention.

(4) *Working Examples:*

As discussed in the Guidance of the Specification section above, Applicant has only shown an example of blocking of the systemic hemodynamic and regional circulatory effects of ET-1 in male normotensive Sprague-Dawley rats with the specific ET_A receptor antagonist that is BQ123, and the increased expression of ET-1 with Aβ treated rats. Applicant has not shown examples for the complete *prevention* of Alzheimer's disease or dementias of vascular origin.

(5) *State of the Art:*

The state of the art regarding the *prevention* of Alzheimer's disease and dementias of vascular origin is underdeveloped. As has been discussed above, Alzheimer's disease is a complex and chronic disease state that has represented a major challenges to academic and pharmaceutical research efforts (see article entitled

"Alzheimer's Disease and Related Dementias: Prospects for Treatment by Williams et al, 1997, Exp. Opin. Invest. Drugs, Vol. 6, No. 6, pages 735-757.) While current treatments include second generation acetylcholinesterase inhibitors, such as donepexil, but such drugs offer only palliative treatment (see abstract of Williams et al, in particular.) The state of the art in the treatment of Alzheimer's indicates that the lack of animal models for the disease remains a large roadblock in finding treatments. In particular, the art teaches "the clinical development of these compounds is hindered by the lack of a widely available animal model which mimics the pathology of AD" (Sheryl J. Hays, "Alzheimer's Disease and Beta-Amyloid Patent Activity between May 1995 and July 1996, Exp. Opin. Ther. Patents, 1996, Vol. 6, No. 10, pages 1035-1046, abstract.) A problem with the development of such *in vivo* models being that such models have to take into account the multifactorial nature of the disease state, as opposed to amyloid neurotoxicity specifically, which "may or may not be causative (see Williams et al, abstract, in particular.) The article entitled "Commentary: Amyloid-Beta Deposits: Can you take them to the Bank?" by Patrick C. May, discloses that much drug development is focused on the fact that "'bad things' are associated with the production and/or accumulation of A-beta peptide and by limiting its production, a therapeutic benefit will be achieved inn AD" (see abstract, in particular.) However, May goes on to disclose that efforts to model this aspect of AD in vivo have so far yielded "ambiguous results" (see abstract, in particular.) Thus, the prior art teaches that treatments for Alzheimer's are as yet unsatisfactory, as the disease is complex and the complete etiology is not yet known.

Reasonable guidance with respect to *preventing* Alzheimer's disease and/or dementias of vascular origin relies on quantitative analysis from defined populations that have been successfully pre-screened and are predisposed to Alzheimer's or dementias of vascular origin. This type of data might be derived from widespread genetic analysis, family histories, correlation of genetic and environmental factors, etc. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of Alzheimer's or dementia onset, and *link* those results with subsequent histological confirmation of the presence or absence of Alzheimer's or dementia. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. As the correlation among factors contributing to Alzheimer's or dementias of vascular origin is not known, the state of the art does not provide a reasonable method of making such a predictive analysis. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease.

(6) *Predictability of the Art*

The invention is directed to the therapeutic treatment or *prevention* of Alzheimer's disease or dementias of vascular origin in *general* with a compound that exhibits endothelin antagonist activity. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved,"

and physiological activity is generally considered to be an unpredictable factor. See *in re Fisher*, 427 F.2d 833, 839 (1970.)

It should also be noted that one of ordinary skill in the art would recognize that it is highly unpredictable in regard to what population will experience Alzheimer's disease or a dementia of vascular origin, as discussed in (5) above. In order to administer the agent to the population at large, one would need to consider the therapeutic effects, side effects and especially potential serious toxicity that may be generated by drug-drug interactions as a result of administration of the claimed compounds to a living organism (e.g., an animal.)

(7) ***The Quantity of Experimentation Necessary:***

In order to practice the disclosed invention, one would need to undergo experimentation to test endothelin antagonist compounds such as those claimed to determine whether or not any of them are actually capable of completely preventing Alzheimer's and dementias of vascular origin, as the instant specification does not show the complete prevention thereof.

As discussed above, the specification fails to provide sufficient support for determining all individuals susceptible to Alzheimer's and/or dementias of vascular origin to allow one or ordinary skill in the art to administer to a population the endothelin

antagonist compounds of the instant invention for the *prevention* of Alzheimer's and dementias of vascular origin in general. As a result, one of ordinary skill in the art would be forced to perform an exhaustive search for the population that is susceptible to Alzheimer's and dementias of vascular origin to use the instant invention.

Genentech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

The Examiner suggests amending the claims to recite a method of providing "medical therapeutic treatment" of Alzheimer's or a dementia of vascular origin by administering the antagonist as claimed to "a mammal having Alzheimer's or a dementia of vascular origin," thereby removing prophylactic, i.e. preventative, treatment from the scope of the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 4, 7, 9 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/17976 to Bolli et al, published March 15, 2001, in view of the article entitled "Recent Discovery and Development of Endothelin Receptor Antagonists" by Chengde Wu, 2000, Expert Opinion on Therapeutic Patents, Vol. 10, No.11, pages 1653-1668.

Bolli et al. teaches the use of compounds having endothelin antagonist for the treatment of various disease states (see page 1, in particular.) Bolli teaches that endothelin antagonist compounds having ET_A and ET_B antagonist activity are suitable for the treatment of conditions known to be associated with an increase in vasoconstriction, proliferation, or inflammation due to endothelin, such as coronary disease, cerebral ischemia, and dementia (see page 2, Table 1 and page 13, lines 1-15, in particular.) Thus, Bolli et al. teaches the treatment of dementias of vascular origin with ET_A and/or ET_B antagonists.

Bolli et al. does not specifically teach providing the particular mixed ET_A/ET_B antagonist corresponding to the elected species of antagonist that is bosentan.

Wu teaches that bosentan is a mixed ET_A/ET_B antagonist that has even been used in clinical trials (see page 1658, section 2.3, in particular.)

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the bosentan of Wu in the treatment of dementia as taught by Bolli et al, because Bolli et al. teaches that dementia associated with endothelin (i.e. of vascular origin) can be treated by providing endothelin antagonists having ET_A and/or ET_B antagonist activity, whereas Wu teaches that bosentan is a compound having known ET_A/ET_B mixed antagonist activity. Thus, one of ordinary skill in the art would have been motivated to provide the bosentan in the method of Bolli et al. with the expectation of providing a compound capable of treating the dementia. Accordingly, claim 1 is obvious over the teachings of Bolli et al. and Wu.

Regarding claims 2, 4, 7 and 9, the teachings of Bolli et al. and Wu render obvious providing bosentan, which compound meets the antagonist activity limitations of the claims. Regarding claim 25, Bolli et al. teaches administering the antagonists to adults and children, i.e. humans (see page 14, lines 19-25, in particular), as recited in the claim.

Claims 13-15 and 19-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/17976 to Bolli et al, published March 15, 2001, in view of the article entitled "Recent Discovery and Development of Endothelin Receptor Antagonists" by Chengde Wu, 2000, Expert Opinion on Therapeutic Patents, Vol. 10, No.11, pages 1653-1668, as applied to claims 1-2, 4, 7, 9 and 25 above, and further in view of U.S. Patent No. 6,037,347 to Schubert et al, issued March 14, 2000.

Bolli et al. and Wu are applied as discussed above, and teach administering the endothelin antagonist that is bosentan for the treatment of dementia. Bolli et al. further teaches that endothelin antagonists can be co-administered with other therapeutic agents, such as ACE-inhibitors (see page 14, lines 5-17, in particular.)

Bolli et al. and Wu do not specifically teach treating dementia with the therapeutic agent corresponding to the elected species of cholinesterase inhibitor that is tacrine, as in claims 13-15.

Schubert et al. teaches the treatment of dementia with compositions containing acetylcholinesterase inhibitors (ACE inhibitors) (see abstract, in particular.) Schubert et al. teaches that such ACE inhibitors treats dementia by affecting the function of nerve and glia cells (see column 1, lines 30-43, in particular.) Schubert et al. teaches that compounds with known ACE-inhibiting activity include tacrine (see column 2, lines 63-65, in particular.)

Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to provide the tacrine ACE-inhibitor of Schubert et al. in the endothelin antagonist dementia treatment method of Bolli et al. and Wu, because Bolli et al. and Wu teach a method of treating conditions such as dementia, and teach that ACE-inhibitors can be combined with endothelin antagonists

to provide treatment, whereas Schubert et al. teaches that tacrine is a ACE-inhibitor that can be used for the treatment of dementia. Thus, it is considered that one of ordinary skill in the art would have been motivated to provide tacrine in the dementia treatment method of Bolli et al. and Wu, with the expectation of providing a compound capable of treatment of the condition. Note it is considered that "[I]t is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980.) Accordingly, claims 13-15 are considered to be obvious over the teachings of Bolli et al. and Wu in view of Schubert et al.

Regarding claims 19-24, Bolli et al, Wu and Schubert et al. render obvious providing a combination therapy of the endothelin antagonist bosentan and the ACE inhibitor tacrine for the treatment of dementia. Accordingly, it is considered that one of ordinary skill in the art at the time the invention was made would have found it obvious to vary and/or optimize the treatment regime, such as by providing the therapeutic agents in the same or separate compositions, or by administering one of the compounds prior to the other, according to the guidance provided by Bolli et al, Wu and Schubert et al, to provide the desired dementia treatment. It is noted that "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454,

456, 105 USPQ 233, 235 (CCPA 1955.) It is furthermore noted that, regarding the order of administration as recited in claims 23-24, it has been held that merely changing the order of steps in a multi-step process is not a patentable modification absent a showing of unexpected results. *Ex parte Rubin* 128 USPQ 440 (POBA 1959.)

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abigail M. Cotton whose telephone number is (571) 272-8779. The examiner can normally be reached on 9:30-6:00, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

AMC

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